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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/670,119	NG ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67-78 and 80-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67-78 and 80-86* is/are rejected.

7)☐ Claim(s) *67,72,82 and 86* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 1996* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location and the examiner of your application in the PTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Zachary C. Howard, Art Unit 1646, Technology 1600.

Status of Application, Amendments and/or Claims

On consideration of the record, and the relevant art, the Examiner finds that this case is not in condition for appeal. In order to address several new grounds of rejection introduced by the claims submitted and entered into the record after final, and to revise the standing enablement rejection in view of several new references found by the Examiner, the finality of the previous Office Action (5/6/2004) is withdrawn. It is noted that a Notice of Appeal and Appeal Brief have been filed. Applicants can request a refund for the associated fee or leave it as credit for future appeals. The delay and inconvenience to Applicants is regretted. It is believed that all of Applicants' arguments presented in the Appeal Brief are addressed in the rejections set forth below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 67-78 and 80-86 are under consideration in the instant application.

Note

The previous set of claims entered in the record was submitted by Applicants on 3/7/05, in the second response filed after the Final Action of 5/6/2004. The Appeal Brief filed 12/8/05 contained a copy of the claims as part of a Claims Appendix. It is noted that the two claim sets are not identical. However, the claims listed in the Appeal Brief are not considered to have been entered as part of the record of the case. Therefore, all rejections set forth below are directed to the most recent set of claims entered on the record (3/7/2005). For Applicants' convenience, the Examiner notes the following

differences between the claims submitted 3/7/2005 and the claims submitted with the 12/8/2005 Appeal Brief. (Differences between the two are underlined by the Examiner.)

Claims 67 and 68: In the 3/7/2005 set of claims, claims 67 and 68 each recite, "...comprising at least sixteen (16) contiguous amino acids..."

However, in the 12/8/2005 Appeal Brief, this same portion of each claim recites, "...comprising at least sixteen contiguous amino acids..."

Claim 68: In the 3/7/2005 set of claims, the concluding phrase recites, "...wherein the peptide contains one or more conservative amino acid substitutions in the nine contiguous amino acids."

However, in the 12/8/2005 Appeal Brief, this same portion of claim 68 recites, "...wherein the peptide contains one or more conservative amino acid substitutions in the sixteen contiguous amino acids."

Claim 86: In the 3/7/2005 set of claims, the claim recites, "...a peptide comprising at least nine contiguous amino acids..."

However, in the 12/8/2005 Appeal Brief, this same portion of claim 86 recites, "...a peptide comprising at least sixteen contiguous amino acids..."

It is noted that Applicants perhaps intended to change all occurrences of "nine" to "sixteen" in the 3/7/2005 set of claims. However, the word "nine" remained in claims 68 and 86 as noted above. While Applicants changed these each occurrence of "nine" to "sixteen" in the Claims Appendix of the 12/8/2005 Appeal Brief, these changes are not considered to be part of the record of the case because they were not part of the last set of claims entered after the final rejection.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

This application is not in sequence compliance for the following reasons:

According the Sequence Listing filed 11/05/1996, SEQ ID NO: 23 is actually a sequence of 25 amino acids that reads:

GVGVGFLAAFILMAVAGNLLVILSV

However, each of claims 67 and 68 was amended 11/3/2004 in the first response after the Final to include the following sequence:

"...GVGVGVFLAAFILMAVAGNLLVILSV (SEQ ID NO: 23)..." which is a new sequence of 26 amino acids. The difference between the two sequences is underlined by the Examiner.

In order for the claims to be compliant with the Sequence Rules, either (1) the claims must be amended to recite the correct sequence for SEQ ID NO: 23 as submitted in the Sequence Listing; or (2) the Sequence Listing must be updated to include the new sequence. However, please note the new rejection under 35 U.S.C. 112, 1st paragraph for new matter set forth below

Specification

The disclosure is objected to because of the following informalities:

1) The title, "RECEPTOR AND TRANSPORTER ANTAGONISTS", of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The claimed invention is directed to peptide antagonists of the alpha-1A adrenergic receptor.

Appropriate correction is required.

Claim Objections

Claims 67, 72, 82 and 86 are objected to because of the following informalities:

(1) Claims 67 and 86 are objected to because they each recite, "...contiguous amino acids residues..." These claims are not grammatically correct. To correct the grammar, they could be amended, for example, to recite, "...contiguous amino acid residues..."

(2) Claim 72 is objected to because the word "conformation" is misspelled as "confirmation".

(3) Claim 82 is objected to because it recites "where in", which is not grammatically correct. To correct the grammar, the claim could be amended, for example, to delete the space such that the claim recites the word "wherein".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, scope of enablement

Claims 67-78 and 80-86 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a method of treating hypertension in a rat in need of said treatment comprising administering a peptide consisting of SEQ ID NO: 31, does not reasonably provide enablement for (1) for treating rats with other peptide sequences, including any sequence comprising at least 9, or at least 16 amino acid selected from SEQ ID NO: 23-29, or comprising conservative amino acid substitutions, side chain modifications, or non-natural amino acids, or (2) for treating any other mammal with any peptide sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is noted that the scope of the enablement rejection set forth herein is different than the scope set forth previously. This change is necessitated by the relevant art made of record below. However, each of Applicants' arguments in response to the previous rejection, as they apply to the instant rejection, are answered below.

Furthermore, claim 80 is herewith included this rejection in view of the change in the scope of the enablement rejection.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are directed to methods of treating hypertension in a mammal in need of treatment comprising administering an effective amount of a peptide. The claims encompass a large number of peptides with different sequences, and treatment of any mammalian species with any of the encompassed peptides. Claim 67 encompasses a peptide comprising at least sixteen amino acid residues selected from one of SEQ ID NO: 23-29. Each of SEQ ID NO: 23-29 is 23, 24, 25, or 26 amino acids. An amino acid sequence of 25 amino acids comprises 10 different sequences of 16 contiguous amino acids, 9 different sequences of 17 contiguous amino acids, 8 different sequences of 18 contiguous amino acids, and so forth, for a total of 55 different peptides consisting of at least sixteen different contiguous amino acids that can be selected from SEQ ID NO: 26 alone. In total, there are 368 different peptides that consist of at least 16 contiguous amino acids regions that are found with SEQ ID NO: 23-26. Furthermore, claim 67 also encompasses innumerable longer sequences comprising each of these 368 different peptides, including the full-length alpha-1A adrenergic receptor. (There is no definition of "peptide" in the specification that places an upper limit on the length of a "peptide")

Claim 68 is similar to claim 67, but broadens the scope to include peptides with one or more conservative amino acid substitutions. As explained in the section "Claim Rejections - 112, 2nd paragraph", the scope of the claim is indefinite but has been interpreted to broadly encompass a conservative substitution in any of the sixteen contiguous amino acids referred to in the claim. Claims 74 and 75 broaden the scope of 67 or 68 to include one or more amino acid residues in the peptide with side chain

modifications (claim 74) or non-natural amino acids (claim 75). Claim 80 narrows the scope to a peptide comprising SEQ ID NO: 31, but still encompass innumerable longer sequences comprising said sequence. Claim 86 broadens the scope of the encompass peptides to those comprising nine amino acids from any transmembrane domain from any alpha-1A receptor from any species of animal. The remaining claims depend from claim 67 or 68 and encompass peptides with the same scope as either of those claims.

While the claims are directed to a large genus of variant peptides, the specification provides only a single working example of a peptide encompassed by this genus. This peptide is SEQ ID NO: 31, which consists of 16 contiguous amino acids found within transmembrane region VII of the rat alpha-1A adrenergic receptor (which is a G-protein coupled receptor or GPCR). The specification teaches (pg 42-43) that administration of a peptide consisting of SEQ ID NO: 31 lowered the heart rate and blood pressure of rats administered phenylephrine (an alpha-1A adrenergic receptor selective agonist). The results were similar to those with the drug prasozin, a previously characterized antagonist of the alpha-1A adrenergic receptor. Therefore, the instant specification is enabled for methods of treatment (of rats) with a peptide consisting of SEQ ID NO: 31, which Applicants have demonstrated is active in antagonizing the receptor.

However, the specification does not enable treatment of hypertension with peptides with a sequence other than SEQ ID NO: 31. The relevant art teaches that it is not predictable which amino acid sequences selected from GPCR transmembrane domains will act as antagonists. Specifically, Tarasova et al (1999) tested the antagonist properties of peptides prepared from each of the seven transmembrane domains (TMs) of the CXCR4 receptor, which is a GPCR (see pg 34912 of Tarasova et al. Journal of Biological Chemistry. 274(49): 34911-34915). Tarasova reports, "In the preliminary screen, peptides corresponding to the second and sixth TMs were found to abolish SDF-1α-induced signaling through CXCR4 receptor" (pg 34912). By altering the length of the peptides and/or substituting amino acids, Tarasova was able to produce antagonists from the second, fourth, sixth and seventh domains. Tarasova reports that they were unable to produce antagonists from the first, third, and fifth membrane

domains ("The results obtained from structure-activity studies were applied to other domains and allowed the identification of antagonists from all but the first, third and fifth TM domains"; pg 34912). Tarasova reports that the peptides from the "first and fifth domains imposed significant synthetic difficulties because of aggregation and turned out to be very poorly soluble." Tarasova further reports that changes of single amino acid residues (either truncations or substitutions) in peptides derived from TM2 altered the antagonist properties of the peptides: "elimination of two C-terminal Asp-residues...decreased antagonist potency more than 10-fold, and substitution of Asp residues with positively charged Lys residues...resulted in a 100-fold decrease in antagonist activity. It is assumed that the charge distribution provides for a proper orientation of the peptides during penetration into the cellular membrane" (pg 34912). In the instant case, the specification provides no guidance as to which (if any) of the transmembrane sequence amino acids can be changed or deleted to yield a functional equivalent of the transmembrane amino acid sequence. Applicants claims specifically include peptides in which only sixteen (or nine) amino acids of the transmembrane domains are present, yet have only shown that a particular peptide from transmembrane region seven can consist of sixteen amino acids. In view of the teachings of Tarasova, it is not predictable that other peptides selected from the transmembrane domains will act as antagonists, and even if the full-length domain acted as an antagonist, it is not predictable that truncated domains would act as antagonist.

With respect to conservative substitutions, Applicants teach on page 11, lines 4-5, "examples of conservative substitutions amino acid substitutions" which include five groups of amino acids. However, there is no limiting definition of the term "conservative". Therefore, the term encompasses amino acid substitutions other than those listed on page 11. Furthermore, the claims encompass peptides in which each of the amino acids of a transmembrane domain is substituted. For example, transmembrane VII is 25 amino acids in length; therefore the claims encompass a genus of peptides corresponding to this domain in which one or more (up to 25) of the amino acids are substituted. The amino acid sequence of a polypeptide determines its

structural and functional properties, and predictability of which amino acids can be substituted or deleted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie *et al.* (1990), *Science* 247: 1306-1310, especially p. 1306, column 2, paragraph 2; Wells (1990), *Biochemistry* 29: 8509-8517). Furthermore, the relevant art has shown that these teachings apply to the transmembrane domains of GPCRs. For example, Baranski et al (1999) identified 14 residues in four transmembrane regions of the C5a GPCR that are intolerant to single amino acid substitutions (see Table II, pg 15763 of Baranski et al. Journal of Biochemistry. 274: 15757-15765). At least six of the single amino acid substitutions are conservative substitutions as taught by Applicants' example, and five others would considered conservative by other definitions (e.g., alanine is substituted for isoleucine or valine, which are all hydrophobic neutral amino acids). Furthermore, these 14 positions are ones in which single amino acid substitutions reduce or eliminate receptor activity, whereas Applicants' claims encompass multiple amino acid substitutions. Since detailed information regarding the structural and functional requirements of the peptide antagonists is lacking, it is unpredictable as to which peptides with substitutions, if any, meet the limitations of the claims. Therefore it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification. The same argument applies to peptides with modified side chains, and peptides with non-natural amino acids, each of which are modifications that change the three-dimensional structure of the amino acid and therefore change its interaction with amino acids in the receptor being antagonized. Furthermore, it is not

predictable what or how many amino acids could be added to one or the other end of the peptides before the additional amino acids would interfere with the antagonist properties of the peptide. Each additional amino acid will change the three-dimensional structure of the peptide. Therefore, the specification is also enabled for peptides comprising SEQ ID NO: 31. Even if a peptide consisting of an entire transmembrane region was shown to have antagonist properties, the specification would not provide enablement for peptides comprising said transmembrane region.

Furthermore, it is not predictable whether or not treatment of a human with a peptide selected from the rat receptor would result in treatment of hypertension. The instant specification teaches, "An antagonist peptide having a transmembrane amino acid sequence of a particular integral membrane protein shows specificity for that protein and does not interfere with the function of closely related integral membrane proteins" (pg 6, starting at line 32). George et al, 2003, further teaches, "An antagonist peptide having the amino acid sequence of the TM domain of a particular integral membrane protein would likely show sequence-dependent specificity for that protein and, as demonstrated in the present work, may not interfere with related proteins" (see pg 488 of George et al. Journal of Pharmacology and Experimental Therapeutics. 307(2): 481-489). Kinsella et al, 2004 teaches the sequence of each of the seven transmembrane domains of the human alpha-1A adrenergic receptor (see Table 1 on pg 917 of Kinsella et al, 2004. Biochemical and Biophysical Research Communications. 324: 916-921). The alpha-1A adrenergic receptor transmembrane sequences taught by Applicant (pg 23) are derived from the rat receptor (Applicants do not specifically state that these transmembrane domains are from a rat receptor sequence; however, these sequences match the rat receptor sequence disclosed in Figure 2 on page 6368 of Lomasney et al, 1991. Journal of Biological Chemistry, 266(10): 6365-6369). A comparison of the transmembrane region VII of the rat and human sequences reveals that the rat sequence of SEQ ID NO: 29 ('EGVFKVIFWLGYFNSCVNPLIYPCS') is different from the human sequence disclosed by Kinsella ('VFKIVFWLGYLNSCINPIIYPCS'). Importantly, the human sequence contains five amino acid differences in the region of similarity to the sequence of SEQ ID NO: 31

('VFKVIFWLGYFNSCVN'), which is the peptide that Applicants have shown to antagonize the rat receptor. Furthermore, the antagonist properties of the peptide are hypothesized to result from the interaction of the peptide from the transmembrane region VII with the rest of the receptor sequence, especially the other transmembrane domains (as taught by George et al (2003), "We propose that the mechanism of action of the TM-based peptides involves their specific interactions with complementary TM domains/segments within the integral membrane protein). Each of the other human transmembrane sequence domains contains differences in the amino acid sequence as compared with the same transmembrane region in the rat sequence. In view of the relevant art (Tarasova et al (1999), cited above) that teaches that changes to the amino acid sequences of the antagonist peptides can alter the function of the antagonist peptide and the relevant art (Baranski et al (1999), cited above), that teaches that the transmembrane regions contain residues sensitive to single conservative substitutions, it is not predictable whether or not the peptide sequence from the rat transmembrane domain VII (SEQ ID NO: 31) would antagonize the activity of the human receptor. Prior to using the rat peptide to treat hypertension in humans, one of skill in the art would first need to experiment to determine whether or not the peptide, when administered to humans, would treat hypertension. Finally, the antagonist properties of any particular sequence selected from the human receptor are not predictable. One of skill in the art would need to experiment to determine what, if any, sequences exist in the human receptor that can be used for antagonism in humans (or rats).

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification which of the claimed peptides, other than those consisting of SEQ ID NO: 31, could be used for treatment of hypertension in rats. There are no examples of treatment of hypertension in rats using a peptide other than SEQ ID NO: 31. Furthermore, it is not predictable which sequences could be used to treat hypertension in humans, and the specification contains no examples of treatment of humans. There is no guidance as to which amino acids could be altered in SEQ ID NO: 31 in order to treat humans. Thus the specification fails to teach the skilled artisan how to use the full scope of the claimed

methods for treatment without resorting to undue experimentation to determine which other peptides would work for treatment of rats and/or humans. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the claimed methods for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the full scope of the claimed peptides could be used for treatment in any mammal, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Applicants' arguments presented at pg 3-4 of the Appeal Brief filed 12/8/05 as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants argue that the specification provides sufficient enablement for the claimed methods. Applicants submit that the amended claims require administration of peptides containing at least sixteen contiguous peptides. Applicants argue that there would be no undue burden for one of skill in the art to identify polypeptides encompassed by the claims. In support, Applicants submit the specification discloses peptides of sixteen amino acids derived from the transmembrane domains of the alpha-1A adrenergic receptor that inhibited drug-induced increases in blood pressure (hypertension). Applicants submit that the Examiner previously indicated the specification was enabling for the claimed peptide sequences that are antagonists to D1 or D2 dopamine receptors, or beta-1 or alpha-1A adrenergic receptors.

Applicants' arguments have been fully considered but are not found persuasive. In view of the relevant art made of record in the present rejection, the previous statements regarding enablement of the claimed peptide sequences is withdrawn. The specification discloses methods of treatment of hypertension with a single species of peptide (SEQ ID NO: 31). The claims encompass a vast genus of peptides with

sequences different from SEQ ID NO: 31. Therefore, as set forth in the above rejection, it would require undue experimentation to test the genus of peptides in order to determine which peptides would or would not be effective in treating hypertension.

With respect to claim 68, Applicants argue that the specification provides guidance as to which amino acids can be changed in said peptide to yield a functional equivalent. In support, Applicants point to the examples of conservative amino acid substitutions disclosed in the specification on page 14, lines 3-10. In view of this, Applicants argue that one of skill in the art could readily determine which conservative substitutions are encompassed by the claims.

Applicants' arguments have been fully considered but are not found persuasive. As set forth above, Applicants provide examples of conservative mutations but do not limit the definition of a conservative mutation to any particular type of mutation. As far as the Examiner can determine, the specification does not even limit the conservative substitutions to those changes that do not affect the activity of the peptide. Applicants argue (in the response to the written description rejection on pg 5) that the specification sets forth at pg 13, lines 6-12, that a peptide with a conservative amino acid substitution must retain activity. However, pg 13, lines 6-12 of the specification relate to carboxyl group modifications, and the Examiner is unable to determine if Applicants are referring to another part of the specification. The specification does not teach which particular amino acid changes can be made at which particular residues in the peptide of SEQ ID NO: 31 and retain activity, and therefore the specification merely invites the skilled artisan to experiment to determine which changes can be made. Applicants argue (in the response to the written description rejection on pg 5) that it is the exception rather than the rule that a single conservative amino acid substitution will change protein function, and that multiple conservative substitutions can generally be made with out changing function. However, Applicants have provided no evidence that multiple conservative amino acid substitutions can be made to peptide antagonist derived from the transmembrane regions of GPCRs, and retain protein functionality. The Examiner has cited a reference teaching that there are particular positions in the transmembrane regions of GPCRs that are intolerant to even single conservative amino acid

substitutions (see Baranski et al, 1999, cited above). Furthermore, Applicants claims encompass multiple substitutions comprising the entire transmembrane region.

Applicants further argue that peptides corresponding to fragments of transmembrane domains are enabled. Applicants submit that evidence in the specification and submitted with the Appeal Brief show that inhibition can be achieved using fragments of transmembrane domains. In support, Applicants submit that the specification teaches that the D2 dopamine receptor can be antagonized using peptides corresponding to fragments of either the VI or the VII domain (page 37, lines 10-22). Applicants argue that the D2 dopamine receptor is used in the specification as a model for other trans-membrane domain receptors. Applicants submit a copy of PCT/CA97/00203 with the Appeal Brief and submit that it provides evidence in support of the enablement of transmembrane domain fragments, particularly a fragment of domain V of the D2 dopamine receptor.

Applicants' arguments have been fully considered but are not found persuasive. It is true that the specification teaches multiple examples of antagonist peptides. However, there are limited teachings with respect to each particular receptor. Two peptides are shown to antagonize the D2 dopamine receptor, one peptide from the TMVI and one from TMVII. With respect to the alpha-1A adrenergic receptor, to which the claimed methods are directed, there is a single example of an antagonist peptide comprising (SEQ ID NO: 31) which is a portion of TMVII. The teachings from the D2 dopamine receptor do not provide sufficient guidance for one of skill in the art to make and use antagonist peptides from the adrenergic receptor. While both are GPCRs, and therefore share some three-dimensional structural similarity, each GPCR has a different amino acid sequence. The relevant art (Tarasova et al, cited above) teaches the unpredictability in selecting antagonist peptides designed from the transmembrane region of another GPCR, CXCR4.

Applicants further argue that "PCT/CA97/00203 also shows that antagonism can be achieved using a peptide which comprises either twenty amino acids from domain VII, or only nine amino acids from domain VII (see page 59, line 10 and page 60, line 10). However, the Examiner notes that page 59, line 10 of PCT/CA97/0020 refers to

"Buffer A" ingredients, and page 60, line 10 refers to "dissociation of the D2 dimer to monomer". There is no specific reference to peptides in either line. Also, Applicants do not make clear what receptor they are referring to. Page 60 appears to discuss D2 receptor peptide antagonists. As stated above, teachings regarding the D2 receptor peptide antagonists are not persuasive as to what peptide antagonists can be made for the alpha-1A adrenergic receptor.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 67-78 and 80-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

The claims are directed to methods of treatment using a highly variant genus of peptides derived from rat alpha-1A adrenergic receptor. Each genus is highly variant because a significant number of structural differences between genus members are permitted. While the specification describes variant peptides, the specification does not describe which variants retain the antagonist activity, other than peptides consisting of SEQ ID NO: 31. Therefore, the instant specification fails to describe the entire genus of peptides that are antagonists that are encompassed by each of the claims.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in

possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of peptides to be used in the claimed methods or cells. There is not even identification of any particular portion of the structure of the peptide of SEQ ID NO: 31 that must be conserved. Structural features that could distinguish other antagonist peptides from others in the encompassed genus are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the

method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only methods comprising administering a peptide consisting of SEQ ID NO: 31, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Applicants' arguments presented at pg 4 of the Appeal Brief filed 12/8/05 as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants argue that the claims meet the written description requirement because the specification provides multiple examples of peptides derived from the transmembrane domains of GPCRs that are effective for modulating G protein receptor activity. Applicants point to the D2 Dopamine Receptor in Example 1 (pg 31). Applicants argue that the "Examiner previously acknowledged that the specification provides sufficient written description for a method of treating a disorder for which administration of a specific antagonist of either the D2 dopamine receptor, β-1 adrenergic receptor or an alpha-1A receptor is effective" in the 8/13/2003 Office Action. Applicants argue that the claims are now limited to peptides comprising at least sixteen amino acids.

Applicants' arguments have been fully considered but are not found persuasive. In view of the relevant art made of record in the present rejection, the previous statements regarding written description of the claimed peptide sequences is withdrawn. The specification discloses methods of treatment of hypertension with a single species

of peptide (SEQ ID NO: 31). The claims encompass a vast genus of peptides with sequences different from SEQ ID NO: 31. Therefore, as set forth in the above rejection, the specification does not provide a written description of the genus of peptides encompassed by the claims. It is true that the specification teaches multiple examples of antagonist peptides to different receptors. However, there are limited teachings with respect to each particular receptor. Two peptides are shown to antagonize the D2 dopamine receptor, one peptide from the TMVI and one from TMVII. With respect to the alpha-1A adrenergic receptor, to which the claimed methods are directed, there is a single example of an antagonist peptide comprising (SEQ ID NO: 31) which is a portion of TMVII. The specific teachings regarding the D2 dopamine receptor do not describe antagonist peptides from the adrenergic receptor. While both are GPCRs, and therefore share some three-dimensional structural similarity, each GPCR has a different amino acid sequence. The relevant art (Tarasova et al, cited above) teaches the unpredictability in selecting antagonist peptides designed from the transmembrane region of another GPCR, CXCR4.

Applicants further argue that the specification sets forth at pg 13 that a peptide with a conservative amino acid substitution must retain activity. Applicants argue that the reference of Townsend-Nicholson is not relevant because the teachings relate to a mutation that alters activity and therefore is not a conservative mutation. Applicants argue that multiple conservative mutations can be made without generally affecting protein function, and it is generally an exception to this rule that a single conservative mutation eliminates activity of a protein.

Applicants' arguments have been fully considered but are not found persuasive. As set forth above, Applicants provide examples of conservative mutations but do not limit the definition of a conservative mutation to any particular type of mutation. Applicants argue that the specification sets forth at pg 13, lines 6-12, that a peptide with a conservative amino acid substitution must retain activity. However, pg 13, lines 6-12 of the specification relate to carboxyl group modifications, and the Examiner is unable to determine if Applicants are referring to another part of the specification. Therefore, as far as the Examiner can determine, the specification does not even limit the

conservative substitutions to those changes that do not affect the activity of the peptide. Therefore, the reference of Townsend-Nicholson remains relevant as teaching that making a single change within one transmembrane domain can have an effect on the receptor's affinity for an antagonist. However, even if the specification does limit conservative substitutions to those that do no affect activity, the specification does not describe which positions can tolerate conservative substitutions, particularly multiple substitutions. Applicants argue that it is the exception rather than the rule that a single conservative amino acid substitution will change protein function, and that multiple conservative substitutions can generally be made with out changing function. However, Applicants have provided no evidence that multiple conservative amino acid substitutions can be made to peptide antagonist derived from the transmembrane regions of GPCRs, and retain protein functionality. The Examiner has cited a reference teaching that there are particular positions in the transmembrane regions of GPCRs that are intolerant to even single conservative amino acid substitutions (see Baranski et al, 1999, cited above). Furthermore, Applicants claims encompass multiple substitutions comprising the entire transmembrane region.

Claims 67-78 and 81-86 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skill in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. Claims 67-78 and 81-86 are drawn to methods of using peptides comprising at least sixteen, or at least nine contiguous amino acid residues, from a transmembrane domain of an alpha-1A adrenergic receptor. However, there are no examples of alpha-1A adrenergic receptor peptides that are nine amino acid residues in length. Furthermore, while there is one example in the specification of a peptide that is 16 amino acids in length, this does not provide written description for the genus "comprising at least sixteen". Furthermore, the concept of the specific genus does not flow naturally from the

disclosure. Therefore, the specification as originally filed lacks support for the genus of molecules encompassed by the amended claims.

Applicants' arguments presented at pg 5 of the 12/8/05 Appeal Brief 12/8/05 as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

Applicants submit that there is adequate written support in the specification for the limitation of a peptide comprising at least sixteen amino acids of SEQ ID NO: 23-29 in the claims. In support, Applicants point to page 8, lines 20-24, which states "antagonist peptides comprising amino acid sequences corresponding to at least four, preferably ten and more preferably from fifteen to twenty consecutive amino acids of an integral protein transmembrane domain." Applicants further point to page 23, lines 11-19, which teaches the transmembrane domain sequences of the alpha-1a adrenergic receptor and page 23, lines 29-34, which teaches that peptides that antagonize the adrenergic receptor are useful for treatment of hypertension.

Applicants' arguments have been fully considered but are not found persuasive. The specification does not provide support for a genus "comprising at least sixteen residues". Applicants teach a range, "comprising...at least four, preferably 10, and more preferably from fifteen to twenty consecutive amino acids". However, a genus may not support a subgenus thought there is a disclosed species with the subgenus. See *In re Smith*, 173 USPQ 679 (CCPA 1972). Furthermore, In *Purdue Pharma L.P. v. Faulding Inc.*, 230F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed. Cir. 2000), the court noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "Ruschig makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure." In the instant case, the specification disclosed peptides comprising fifteen to twenty consecutive amino acids, and there is no guidance directing the skilled artisan to peptides comprising at least sixteen amino acids, despite the single disclosure of a species of sixteen amino acids. Furthermore, the claimed genus of peptides "comprising at least sixteen" includes peptides comprising sixteen or

more residues, including those over twenty (up to the length of SEQ ID NO:23-29, which vary in length from 23-26 amino acids). However, the genus disclosed in the specification comprising fifteen to twenty amino acids does not provide a written description for peptides comprising more than twenty residues, as is included in current claims. See *In re Wertheim*, 541 F. 2d 257, 191 USPQ (CCPA1976). In this case, the ranges described in the original specification included a range of "25%-60%" and specific examples of "36%" and "50%". A corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range."

Claims 67-78 and 81-85 also lack written description for the following sequence, which is considered new matter: "GVGVGVFLAAFILMAVAGNLLVILSV" (emphasis added by examiner). Claims 67 and 68 each recited said sequence, and the other claims depend from 67 or 68. However, this specific sequence is not present in the specification as originally filed. Therefore, the specification as originally filed lacks support for molecules with this sequence, as encompassed by the claims. It is noted that Applicants perhaps intended to recite the sequence of SEQ ID NO: 23 ("GVGVGFLAAFILMAVAGNLLVILSV") in each of claims 67 and 68.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-78 and 80-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 68 is indefinite because it first recites, "...a peptide comprising at least sixteen (16) contiguous amino acids..." and then later recites, "...wherein the peptide contains one or more conservative amino acid substitutions in the nine contiguous

amino acids." This is indefinite for two reasons: (1) the number of contiguous amino acids do not match and therefore the Examiner is unable to determine exactly what is being claimed; (2) the reference to "...the nine contiguous amino acids..." lacks antecedent basis within the claim. For purposes of prosecution, and because "nine" falls within "sixteen", this claim has been interpreted to encompass conservative amino acid substitutions in any of the sixteen contiguous amino acids.

Claim 80 is indefinite because it recites "...wherein the amino acid sequence of the peptide is selected from the group consisting of: VGFKIFWLGYFNSCVN (SEQ ID NO: 31)." This is indefinite because the claim indicates there is a group from which the peptide will be selected from, but then sets forth a single peptide rather than a group. Markush-type claims should be set forth as indicated at MPEP 803.02 [R-3] "Markush Claims", which states, "A Markush-type claim recites alternatives in a format such as "selected from the group consisting of A, B and C."

The remaining claims are rejected for depending from an indefinite claim.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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